

## **REMARKS**

### **I. Claims in the Case**

Independent claim 54 has been amended and is now directed specifically to the use of 4HPR lipid compositions wherein the lipid composition comprises DMPC and water. Claims 133 and 138 have been cancelled and the dependencies of claims 134 and 139 revised accordingly.

Applicants are amending independent claim 54 in order to prosecute the claimed subspecies of allowance/appeal. Applicants reserve the right to proceed with claims directed to the additional subject matter in future continuing applications. If the pending claims are passed to allowance, Applicants would propose to cancel withdrawn claims 61-119 and 130, or authorize an examiner's amendment, in order to place the case into condition for allowance.

### **II. Rejections Under 35 U.S.C. §103**

All of the claims have again been rejected over Mehta in view of Ulukaya (claims 54-56) or in view of Minton or Zeligs (claims 54-60). The Action takes the position that Mehta teaches liposomal formulations of retinoids in combination with DMPC and soybean oil. Ulukaya is cited as teaching that 4-hydroxyphenyl retinamide (4-HPR) has various advantages over naturally occurring retinoids, including fewer side effects. Minton and Zeligs are cited as teaching other advantages to 4-HPR.

In response, Applicants would note that the principal reference, Mehta, fails to teach or suggest the use of DMPC and water to form its liposomes. Mehta's Example 1 describes the preparation of liposomal-all trans-retinoic acid ("L-RA"). In the paragraph beginning at col 7, line 54 of Mehta, it is described that the retinoic acid ("RA") is comprised in t-butanol, and that the butanol-solubilized RA is then added to the "dried lipid film" to form the liposomes. There

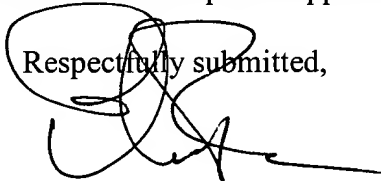
is no teaching here that water or an aqueous solution is added during the liposomal formulation step.<sup>1</sup> In contrast, Applicants' specification discloses, for example in Example 1 and Table 2 (page 83), that liposomal 4-HPR can be formed using DMPC and water, or DMPC + water + soybean oil ("SO"). Importantly, the encapsulation efficiency achieved by the present inventors for 4-HPR using water or water + SO was consistently very high: 81.5% with DMPC + water and ranging from 77.5% up to 96.4% with DMPC + water + SO. This was in direct contrast to the much poorer 60% encapsulation efficiency achieved without the inclusion of water.

The secondary references relied upon by the Examiner do not appear to cure this deficiency in the rejection.

Thus, for the foregoing reasons, it is respectfully submitted that the Examiner has failed to make a *prima facie* case of obviousness and that the invention is shown to be surprising unexpected in light of the prior art.

The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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<sup>1</sup> While Mehta does disclose "reconstitution" of already-formed "liposomal retinoic acid" in an aqueous solution (see, *e.g.*, col. 7, ln 66, to col. 8, ln 3) it does not appear that there is any teaching of actually forming the liposome using water with the lipids.